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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,432	BUSCHMANN ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 March 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 4/2/03, as Paper No. 10. The amendment has been entered. Claims 8, 9, 13-20, 22 and 23 have been cancelled. Claim 1 has been amended. Claims 1, 3, 4, 6 and 10-12 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Drawings

3. New corrected drawings are required in this application for the reasons of record. Applicants have indicated that corrected drawings are forth coming. Applicants are reminded that the corrected drawings are required in **reply to this Office action to avoid ABANDONMENT** of the application. The requirement for corrected drawings **will not be held in abeyance**.

Specification

The objection to the specification is withdrawn in view of the amendment removing the active hyperlink.

Claim Rejections - 35 USC § 112, second paragraph

The rejection of claims 1, 3, 4, 6 and 8-12 under 35 USC 112, second paragraph are withdrawn in view of the amendment.

Claim Rejections - 35 USC § 112, first paragraph

The rejection of claims 1, 3, 4, 6 and 8-12 under 35 USC 112, first paragraph (written description) are withdrawn in view of the amendment. However, the rejection of claims 1, 3, 4, 6 and 10-12 under 35 USC 112, first paragraph (enablement) are not obviated by the amendment. The pending rejection is reiterated below.

4. Claims 1, 3, 4, 6 and 10-12 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for enhancing arteriogenesis and/or the growth of collateral arteries and/or other growth of other arteries from said collateral arteries in mammals, wherein the method comprises delivery of TGF-beta 1 polypeptide directly to preexisting arteries of said mammals, does not reasonably provide enablement for the method wherein a TGF-beta 1 derivative or functionally equivalent molecule is administered, or wherein the TGF-beta 1 is not locally delivered into the collateral circulation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for enhancing arteriogenesis and/or growth of collateral arteries and/or other arteries from preexisting arteriolar connections by administering TGF-beta1 polypeptide or a derivative or functionally equivalent molecule. Therefore, the nature of the invention is modulation of arteriogenesis/artery growth for therapeutic purposes by administration of a pharmaceutically active compound.

The breadth of the claims

The breadth of the claims is very broad. For instance the claims encompass administering any TGF-beta 1 polypeptide derivative or functionally equivalent substance, for treating any vascular disease or cardiac infarct in any species of animal, including humans.

The unpredictability of the art and the state of the prior art

There are a number of problems recognized in the art with respect to administration of a protein pharmaceutical for treatment of disease, and specifically with the treatment to enhance arteriogenesis.

For instance, Shire in Biopharmaceutical Drug Design and Development (Wu-pong et al. Eds, Humana Press; Chapter 9; pages 205-238) teaches some of the problems associated with protein as pharmaceutical agents. Specifically, Shire teaches,

> "The formulation of protein therapeutics is more difficult than for traditional small-molecule drugs, because of the complex composition and physical properties of the proteins. In particular, the importance of maintaining protein confirmation makes this task especially difficult. Loss of protein activity or increased immunogenicity can result without any covalent chemical modifications. Many of the degradative pathways in proteins, such as proteolysis, deamidation, oxidation, or self-association, will be subject to a diverse set of solution conditions. Generally, especially for a liquid formulation, it is not possible to produce a formulation that will eliminate all of the potential routes of inactivation." See paragraph bridging pages 231-232.

Scholz et al. (Angiogenesis Vol. 4; p. 247-257; 2001) indicates the unpredictable nature of arteriogenesis as a therapeutic method for treating vascular diseases. Specifically, Scholz teaches,

"Collateral vessels exhibit the same morphology whether they had formed in the heart, limbs or brain or in dogs, rabbits or mouse. They are tortuous because they also increase lengthwise in a restricted space. In animals larger than the mouse, they develop an intima, and initially, many arterioles participate in arteriogenesis, but only a few mature into large arterial channels which, when arterial occlusion had preceeded slowly enough, can replace the occluded artery to a significant proportion. Therapy with a single growth factor in animals with occluded femoral arteries significantly increased the speed of arteriogenesis but does not significantly increase the level of adaptation. It appears that the master gene for arteriogenesis still awaits discovery." (See p. 247, abstract).

Therefore, it is unpredictable that a protein therapy could be effectively used to treat any vascular disease.

Working Examples and Guidance in the Specification

The specification indicates one example where TGF-beta polypeptide (0.48 ug/kg/day) was locally administered directly into the collateral circulation of rabbits comprising a femoral artery ligation (see example 3, p. 20-23). It is disclosed that "TGF-beta 1 infusion for a time period of one week had significantly increased the number of visible collateral arteries as compared to the PBS-control group... The results of the experiments performed in accordance

with the present invention indicate that TGF-beta 1 is capable of mediating arteriogenesis, and/or the growth of collateral arteries and/or other arteries from preexisting arteriole connections by activation of the monocyte/macrophage pathway" (see p. 22, second and third paragraphs).

There is no indication that administration of the TGF-beta 1 polypeptide by any means other than direct delivery into the collateral arteries can stimulate arteriogenesis and/or growth of collateral arteries and/or growth of other arteries from said collateral arteries. Furthermore, there is no indication that the treatment could effectively treat any vascular disease such as cardiac infarct or stroke.

Quantity of Experimentation

Additional experimentation is required in order to overcome unpredictable nature of protein therapy in general and the unpredictable nature of therapeutic arteriogenesis recognized in the art and effectively use the claimed method to the full scope encompassed by the claims. For instance, experimentation would have to be done in order to effectively deliver a protein therapeutic agent by any means other than direct delivery in order to avoid protein degradation pathways (and the hosts immune response). Furthermore, one would have to show that the administration could effectively stimulate enough arteriogenesis or collateral (or other) artery growth effective to treat any vascular disorder including cardiac infarct, stroke, etc.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability recognized in the art, the breadth of the claims, the limited of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Response to Arguments

5. Applicant's arguments filed 4/2/03 have been fully considered but they are not persuasive. Applicants contend that the rejection was based on the use of TGF-beta1 derivatives and functionally equivalent substances and argue that the amendment, which narrows the scope of the claims so that the claims do not encompass derivatives and functionally equivalent substances should obviate the pending rejection.

In response, it is respectfully pointed out that the claims were rejected under 35 USC 112, first paragraph (enablement) not only because the claims encompassed TGF-beta derivatives and functionally equivalent substances, but also because of the problems associated with administration of a therapeutic polypeptide to a subject by any rout of administration. As previously set forth, the claims are only enabled for the method where the therapeutic polypeptide is administered directly to the collateral arteries of the mammals. It is respectfully pointed out that the claims have not been limited to directly administering the TGF-beta polypeptide to the target existing collateral arteries. Therefore, the rejection is not withdrawn.

New Grounds of Rejections

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3 and 10-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Roberts et al. (PNAS 1986; Vol. 83, p. 4167-4171).

The instant claims are drawn to a method for enhancing arteriogenesis and/or the growth of collateral arteries and/or other arteries from preexisting arteriolar connections comprising contacting an organ, tissue or cells with TGF-beta polypeptide.

8. Roberts teaches a method wherein TGF-beta polypeptide is administered to newborn mice by delivering the TGF-beta polypeptide directly to existing blood vessels by subcutaneous injection, resulting in the induction of angiogenesis from preexisting blood vessels and rapid activation of fibroblasts to produce collagen in the area of injection (e.g., see abstract; p. 4167, col. 1; and p. 4168, under "In Vivo Studies").

Regarding the term "angiogenesis" it is respectfully pointed out that Merriam Webster's Collegiate Dictionary, Tenth Ed. Defines angiogenesis as, "the formation and differentiation of blood vessels." (See p. 44). Therefore, the term "angiogenesis" encompasses the formation of any type of blood vessel, including arteries. Although Roberts does not explicitly indicate if the method results in the formation of collateral arteries or other arteries from preexisting arteriolar

connections, the fact that Roberts teaches that the method results in induction of angiogenesis indicates that the method results in the formation of blood vessels.

Furthermore, the method of Roberts appears to be identical to the claimed method. Identical methods would have identical results. Although Roberts does not explicitly indicate that administration of TGF-beta results in enhanced arteriogenesis and/or the growth of collateral arteries and/or other arteries from preexisting arteriolar connections, the method steps taught by Roberts are identical to the claimed method steps. Therefore, the method of Roberts would inherently have the same results as the claimed method.

It is noted that claim 10 is drawn to the method of claim 1 wherein said method is applied to a subject from a vascular disease or cardiac infarct or stroke; claim 11 is drawn to the method of claim 10 wherein said vascular disease is arteriosclerosis and/or other diseases; and claim 12 is drawn to the method of claim 1 wherein the method is applied to a subject during or after exposure to an agent that damages or destroys arteries. Regarding claims 10-12 it is respectfully pointed out that these claims merely set forth intended uses for the method and do not add any patentable weight to the claimed method. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. Here, there is no difference between the claimed method and the method of Roberts; therefore, the method of Roberts is capable of performing the intended use.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roberts et al. (PNAS 1986; Vol. 83, p. 4167-4171) in further view of Asahara (Circulation, 1995, Vol 92 (9, Suppl.) pages II365-371).

Claim 1 is rejected based on the teaching of Roberts for the reasons set forth above.

Roberts teaches a method of inducing angiogenesis/arteriogenesis by administering a TGF-beta polypeptide to a mammalian subject, as mentioned above.

Roberts does not teach that the method further comprises contacting the organ, tissue or cells with a growth factor or cytokine (claim 4); wherein said growth factor or cytokine is b-FGF, PDGF, TNF-alpha, IL-1, IL-6 or VEGF (claim 6).

However, Asahara teaches a method for inducing angiogenesis by administering a combination of two angiogenic molecules: b-FGF and VEGF. Asahara teaches that the combination treatment of b-FGF and VEGF has a synergistic effect on angiogenesis in vivo. Specifically, Asahara teaches,

> "Combined administration of VEGF and bFGF stimulates significantly greater and more rapid augmentation of collateral circulation, resulting in superior hemodynamic improvement compared with either VEGF or bFGF alone. This synergism of two angiogenic mitogens with different target cell specificities may have important implications for the treatment of severe arterial insufficiency in patients whose disease is not amenable to direct revascularization." (See Abstract)

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the method of inducing angiogenesis using TGF-beta taught by Roberts such that the method comprised administration of TGF-beta and VEGF or b-FGF with a reasonable expectation for success.

The motivation to modify the method taught by Roberts is provided by Asahara, who indicates that combinations of angiogenic mitogens may have important implications for the treatment of sever arterial insufficiency in patients whose disease is not amenable to direct revascularization.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
June 15, 2003